QM/MM Kinetic Isotope Effects

for Chloromethane Hydrolysis in Water

J. Javier Ruiz Pernía,[a,b] Giuseppe D. Ruggiero[a] and Ian H. Williams[a *]

[a] *Department of Chemistry, University of Bath, Bath, UK BA2 7AY*

[b] *Departament de Química Física i Analítica, Universitat Jaume I, 12071 Castelló, Spain*

Abstract:

Computational simulations for chloromethane hydrolysis have been performed using hybrid QM/MM methods with explicit solvation by large numbers of water molecules. In the first part of the paper we present results for 2° $^{2}H_3$, 1° ^{14}C and 1° ^{37}Cl kinetic isotope effects (KIEs) at 298 K with both the AM1/TIP3P and B3LYP/6-31G* QM methods for the nucleophile H_2O and electrophile CH_3Cl surrounded by 496 solvating TIP3P water molecules. An initial Hessian computed for a subset of this system including up to 104 MM water molecules was reduced in size by successive deletion of rows and columns, and KIEs evaluated for each. We show that for accurate calculations of KIEs in solvated systems should involve a subset Hessian including the substrate together with any solvent atoms making specific interactions with any isotopically substituted atom. In the second part of the paper, the ensemble-averaged 2° α-$^{2}H_3$ KIE calculated with the B3LYP/6-31+G(d,p)/TIP3P method is shown to be in good agreement with experiment. This comparison is meaningful because it includes consideration of uncertainties owing to sampling of a range of representative thermally-accessible solvent configurations. We also present ensemble-averaged ^{14}C and ^{37}Cl KIEs which have not as yet been determined experimentally.

Introduction

One of us (IHW) first met Rory More O'Ferrall at the 1979 Gordon Research Conference on Isotope Effects (having encountered the eponymous diagram in undergraduate lectures five years earlier) and later it was Rory who introduced us to the Kyushu International Symposia on Physical Organic Chemistry. At the 1999 KISPOC, we presented results of hybrid quantum-mechanical/molecular-mechanical (QM/MM) calculations for the secondary α-^{2}H kinetic isotope effect (KIE) $k(^{1}H_3)/k(^{2}H_3)$ for chloromethane hydrolysis.[1] This work used the conventional approach in which molecular partition functions were evaluated for isotopologues of a single transition structure (TS) and single reactant structure (RS) connected to the former by an intrinsic reaction coordinate path. The 8 QM

(AM1, HF/3-21G, HF/6-31G* or MP2/6-31G*) atoms of the nucleophile and electrophile, H_2O + CH_3Cl, were surrounded by a sphere of several hundred MM (TIP3P) water molecules, and our GRACE algorithms[2] were used to locate and characterize the energy minimum and the saddle-point for each QM method. Superficial comparison of the computed $\Delta^{\ddagger}H$ and α-$^2H_3$ KIE values with experiment[3,4] (Table 1) showed best agreement for MP2/6-31G* and worst for AM1 (in the first configuration considered), but consideration at several different RS/TS pairs determined at the AM1/TIP3P level with different solvent configurations (#1 to #5) showed that the variation in KIE values was at least as great as that between different QM methods. This finding suggested to us that comparisons of calculated and observed KIEs for reactions in explicit solution were, in general, likely to be either meaningless or fortuitous unless appropriate averaging over solvent configurations were performed. However, at that time we did not know how to do this averaging correctly. For example, should a simple arithmetic mean of the KIEs be taken, or should the average be Boltzmann-weighted according to the value of $\Delta^{\ddagger}H$? But the total QM/MM energies for the solvated RSs (or product structures) varied over a range of about 27 kJ mol^{-1} whereas those for the solvated TSs varied by only about 4 kJ mol^{-1} (Table 1): should the reactant and transition *states* be considered independently?

Recently we reported ensemble-averaged QM/MM KIEs for the S_N2 reaction of cyanide anion with chloroethane in DMSO solution at 30 °C.[5] Best results were obtained as the ratio $\langle f_{RS}\rangle/\langle f_{TS}\rangle$ of isotopic partition function ratios (IPFRs) separately averaged over all RS and TS configurations. In this way the hybrid AM1/OPLS-AA potential yielded average ⟨KIE⟩ values for six isotopic substitutions (2° α-$^2H_2$, 2° β-$^2H_3$, α-^{11}C/^{14}C, leaving group ^{37}Cl, and nucleophile ^{13}C and ^{15}N) for this reaction in the correct direction as measured experimentally. These thermally-averaged calculated KIEs could be compared meaningfully with experiment, and only one of them differed in magnitude from the experimental value by more than one standard deviation from the mean. This success contrasted with previous KIE calculations based upon traditional methods without averaging. The IPFRs were best evaluated using all $3N_s$ vibrational frequencies obtained from Hessians determined for subsets of N_s atoms, relaxed to local minima or saddle points, within frozen solvent environments of structures sampled along molecular dynamics trajectories for RS and TS.

Here we present results from computational simulations for chloromethane hydrolysis using QM/MM methods with explicit solvation by large numbers of water molecules. First, we discuss the notion of a "cutoff rule" for QM/MM calculations of KIEs for reactions with explicit solvation. Second, we discuss ensemble–averaged KIEs calculated by means of the same procedure described in detail elsewhere.[5]

$$H_2O + CH_3Cl \rightarrow [H_2O\cdots CH_3\cdots Cl]^{\ddagger} \rightarrow {}^{+}H_2O\text{–}CH_3\cdots\cdots Cl^{-}$$

Methodology

A cutoff rule for KIEs of reactions in aqueous solution

A standard procedure to simplify computations in the early days of KIE calculations was to employ the cutoff rule first introduced by Stern and Wolfsberg:[6] it was possible to leave out parts of a "large" molecule without significantly affecting the value of a calculated KIE, provided that (a) it was around room temperature, (b) the omitted atoms were more than two bonds distant from the position of isotopic substitution where force constants changed from the reactant structure to the transition structure, and (c) the force constants for that portion of the molecule retained were correct (i.e. the same as they would be in the whole molecule without the cutoff).[7]

Now that QM/MM calculations of KIEs in explicit solvent have become feasible,[8,9] there is no need to truncate the structures of reacting systems in the original Stern-Wolfsberg manner, as it is possible to treat systems containing very large numbers of atoms. However, decisions do need to be made in regard to the extent of both the QM and MM regions and the size of the subset of atoms included in a subset Hessian determination. (Often the subset is the same as the QM region, but this is not a necessary condition: it could be either larger or smaller.) Moreover, in order to obtain reliable calculated KIEs, it is important to ensure that the sizes of both the whole system and the subset are adequate to provide satisfactory evaluation of both the potential energy and kinetic energy contributions to the isotopically-affected vibrational motions. The potential energy contribution is described (within the harmonic approximation) by the values of matrix elements of the Hessian (*i.e.* the magnitudes of the force constants mentioned in criterion (c) above) which depend upon the nature of the QM/MM potential: primarily the quality of the QM method and of the QM/MM interface. For example, it is essential include the influence of a solvent environment in order to describe KIEs accurately for a reaction in solution: it is not appropriate to use gas-phase force constants as these do not include the effects of solvation. The kinetic energy contribution is more subtle and describes the dynamical coupling between isotopically-substituted atoms and their environment within a solvated system.

To the extent that KIEs may be treated to a satisfactory degree of approximation by means of cutoff" procedures, it implies that these ratios of rate constants are essentially local properties of the system, reflecting changes in curvature of the potential energy surface in the immediate vicinity of the position(s) of isotopic substitution. However, since the Stern-Wolfsberg cutoff rule was formulated for molecules in which the omitted atoms were covalently linked to the retained atoms, the systems now

typically studied by QM/MM methods involve noncovalent solvent−solute interactions, and it is timely now to enquire what form of cutoff rule is appropriate for such systems.

In one series of investigations, AM1/TIP3P Hessians were computed for the $N_q = 8$ QM atoms of either RS or TS plus a varying number ($0 \le m_w \le 104$) of MM water molecules (maximum size 960 × 960); see Figure 1. In another series, B3LYP/6-31G*/TIP3P Hessians were similarly computed for the QM atoms plus a varying number ($0 \le m_w \le 60$) of MM water molecules. The remaining ($496 - m_w$) excluded water molecules influenced the values of the force constants for the m_w included waters, as well as their geometrical positions, by means of the network of hydrogen-bonding interactions. Starting from the largest Hessian ($N_s = N_q + 3m_w = 320$ atoms), a series of calculations was then carried out in which water molecules furthest from RS or TS were removed from the kinetic energy term for the normal modes of vibration: this was performed by deletion of the corresponding rows and columns of the large Hessians. This process was continued until only the $N_q = 8$ QM atoms of either RS or TS were included in cutoff Hessians of dimension 24 × 24. It is important to understand that the retained elements of each Hessian were unchanged from their values in the large Hessian. Although the calculations were actually carried out in mass-weighted Cartesian coordinates (for which the kinetic energy is represented simply by the unit matrix), this procedure is equivalent to keeping the potential energy matrix **F** unchanged while eliminating atoms from the kinetic energy matrix **G** of the traditional Wilson formalism.[10]

Within transition-state theory, the semiclassical KIE is given by eq. 1, where Q^{RS} and Q^{TS} are molecular partition functions for RS and TS species, respectively. If translations, rotations and vibrations are considered as separable motions, each Q is the product of q_{trans}, q_{rot} and q_{vib}: the latter term is evaluated over $3N - 6$ modes for RS and but $3N - 7$ modes for TS. Re-arrangement of the partition-function factors on the middle-left-hand side of eq. 1 yields a ratio ("RS over TS") of IPFRs ("heavy over light"), f_{RS} and f_{TS}. Note that this expression for the KIE does not explicitly include the ratio of isotopic transition frequencies $(\nu_{light}/\nu_{heavy})^{\ddagger}$; its effect is implicitly included within q_{trans} and q_{rot} values for the light and heavy RS and TS species.

$$KIE = \frac{(Q^{TS}/Q^{RS})_{light}}{(Q^{TS}/Q^{RS})_{heavy}} = \frac{(Q_{heavy}/Q_{light})^{RS}}{(Q_{heavy}/Q_{light})^{TS}} = \frac{f_{RS}}{f_{TS}} \quad (1)$$

KIEs were obtained for four isotopic substitutions (2° α-$^{2}H_3$, α-^{14}C, leaving group ^{37}Cl and nucleophile ^{18}O), with the IPFRs being determined by a procedure which ignored all coupling between the subset atoms and their environment. This employed a projection to eliminate the 6 librations of the

N_s subset atoms as translational and rotational modes with zero eigenvalues, leaving $3N_s - 6$ genuine vibrations which satisfied the Teller-Redlich product rule[11] for isotopologues, being entirely consistent with the masses and moments of inertia obtained from the molecular geometries of the subset atoms alone. Each KIE in this study represented the ratio f_{RS}/f_{TS} of IPFRs for a single pair of RS and TS configurations.

Ensemble–averaged KIEs for reactions in aqueous solution

The key features of our procedure for ensemble averaging of KIEs are as follow. First, we perform QM/MM molecular dynamics (MD) simulations at the desired temperature for RS and TS; the TS is subject to a constraint to prevent it collapsing to the RS or product. Next, we extract numerous independent configurations from the RS and TS trajectories. For each "snapshot", we perform QM/MM geometry optimisation to either a local minimum or saddle-point within a frozen environment. The advantage of allowing each snapshot structure to optimize only to a local minimum within a frozen configuration of the environment is that each different structure is more likely to be representative of the whole system at the temperature of the simulation. In contrast, if for each snapshot the whole system is minimised,[12] then the configuration of the environment changes to something corresponding to a much lower temperature and which is unrepresentative of the real system. The method should capture the effects of specific interactions between a substrate and its environment that a continuum model is incapable of doing (for solutes in solution).

Finally we compute the QM/MM Hessian for a subset of selected atoms within the relaxed region and calculate the average $\langle KIE \rangle_{state}$ (eq. 2) as the quotient of the average IPFR for the reactant state (eq. 3) as dividend with the average IPFR for the transition state (eq. 4) as divisor. All Ω_{RS} RSs are considered as a reactant-state ensemble and all Ω_{TS} TSs as a transition-state ensemble. This method is based on the assumption that the reactant state and the transition state are entirely independent, which is entirely consistent with conventional transition-state theory.

$$\langle KIE \rangle_{state} = \langle f_{RS} \rangle / \langle f_{TS} \rangle \tag{2}$$

$$\langle f_{RS} \rangle = \frac{1}{\Omega_{RS}} \sum_{i}^{\Omega_{RS}} (f_{RS})_i \tag{3}$$

$$\langle f_{TS} \rangle = \frac{1}{\Omega_{TS}} \sum_{j}^{\Omega_{TS}} (f_{TS})_j \tag{4}$$

We recently pointed out that with subset Hessians it is better to compute IPFRs by means of eqs. 5 and 6 which include coupling between the N_s subset atoms and their environment:[13] note the products are taken over the $3N_s$ and $3N_s - 1$ real vibrational frequencies of each RS and TS, respectively.

$$(f_{RS})_{subset} = \prod_{i}^{3N_s} \frac{\sinh(u_i^{RS}/2)_{light}}{\sinh(u_i^{RS}/2)_{heavy}} \quad (5)$$

$$(f_{TS})_{subset} = \prod_{i}^{3N_s-1} \frac{\sinh(u_i^{TS}/2)_{light}}{\sinh(u_i^{TS}/2)_{heavy}} \quad (6)$$

Within the limits of the harmonic approximation, it is logical also to include a quantum correction to the partition function for motion in the transition vector with its imaginary frequency (*i.e.* tunneling). The tunneling correction to the KIE may be obtained approximately by means of Bell's expression for an inverted parabola, eq. 7. [14]

$$(f_{TS})^{QC}_{subset} = \left[\frac{\nu_{heavy}}{\nu_{light}}\right]^{\ddagger} \frac{\sin(u_i^{TS}/2)_{light}}{\sin(u_i^{TS}/2)_{heavy}} \times (f_{TS})_{subset} \quad (7)$$

In the event that the relaxation of the subset atoms to a local minimum or saddle point within their frozen environment yielded any residual small imaginary frequencies (not including the transition frequency for a transition structure), each of these was replaced by a real frequency of the same magnitude. This procedure is recommended for the following reason: owing to the non-separability of the internal and external modes, some of these small imaginary frequencies are isotopically sensitive to a (perhaps) surprising extent, such that their omission can cause the IPFR for that particular configuration to become <1, which is unphysical and incorrect. Furthermore, omission leads to larger standard deviations in the IPFR values and KIEs, whereas replacement by real frequencies appears to capture the isotopic sensitivity correctly and ensures that the vibrational product of all $3N_s$ isotopic frequency ratios is numerically equal to the isotopic mass-ratio factor as it is required to be.

Results and Discussion

A cutoff rule for KIEs of reactions in aqueous solution

Tables 2 and 3 contain QM/MM calculated results for 2° $^2H_3$, 1° ^{14}C and 1° ^{37}Cl kinetic isotope effects at 298 K for chloromethane hydrolysis with, respectively, the AM1/TIP3P and B3LYP/6-31G* QM methods for the nucleophile H_2O and electrophile CH_3Cl surrounded by 496 solvating TIP3P water molecules. Inspection of these Tables reveals little change to either the overall KIEs or their mass-moment-of-inertia (MMI), excitational (EXC) and zero-point-energy (ZPE) factors[14] as the

surrounding water molecules retained in the Hessian are diminished to a single-digit number, corresponding to only those directly hydrogen-bonded to the nucleophile and leaving group in the TS for chloromethane hydrolysis, $[H_2O^{\cdots}CH_3^{\cdots}Cl]^{\ddagger}$. As even these are stripped away, so the balance between MMI, EXC and ZPE is affected due to changes in the isotopic sensitivities of the rigid-rotor and harmonic-oscillator partition functions[14] for rotation and vibration as the size and shape of the system changes. The use of eq. 1 to calculate the KIE in terms of 3 translation, 3 rotational and $3N_s - 6$ vibrational degrees of freedom for RS and for TS is equivalent to removing the N_s subset atoms from their solvent environment completely and treating them as a gas-phase cluster instead. Although the potential energy contribution to the vibrational motion is calculated using force constants from the fully solvated system, the kinetic energy contribution involves only the small subset of atoms.

The AM1 results (Table 2) suggest (fortuitously) that the products KIE = MMI × EXC × ZPE are hardly changed from $N_w = 104$ to $N_w = 0$ for each of the isotopic substitutions, whereas the B3LYP results (Table 3) show a dramatic change in the $^2H_3$ KIE, in particular, as N_w decreases from 5 to 2 and then to 0. A similar study for the chorismate rearrangement in water,[15] performed contemporaneously with these calculations, shows significant changes associated with removal of first-solvation-shell waters that make specific interactions with atoms of the reacting substrate. More recently we showed that errors in calculated KIEs, associated with similar changes in the size of the subset Hessian, were much lower when $3N_s$ vibrational frequencies were used than when $3N_s - 6$ projected vibrational frequencies were used together with masses and moments of inertia for the subset in isolation.[12] This suggests that the 6 "librations" of the subset with respect to its environment contain isotopically sensitive information that should not be excluded from KIE calculations. Thus, for S_N2 methyl transfer from *S*-adenosylmethionine to catecholate anion in water,[12] eqs. 5 and 6 were used to compute KIEs as quotients f_{RS}/f_{TS} of IPFRs involving all $3N_s$ frequencies (vibrations + librations) of the subset. Nonetheless, the final conclusion was the same: regardless of considerations of the choice of QM/MM method, for accurate calculations of KIEs in large systems it was recommended to select a subset of atoms including all covalently-bonded atoms to a distance of at least three bonds from any isotopically substituted atom (the Stern-Wolfsberg cutoff) together with any solvent atoms making specific interactions with any isotopically substituted atom.

Ensemble–averaged KIEs for reactions in aqueous solution

Table 4 contains ensemble-averaged QM/MM 2° $^2H_3$, 1° ^{14}C and 1° ^{37}Cl kinetic isotope effects for chloromethane hydrolysis at 300 and 363 K calculated by means of eqs. 2 – 7. The semiclassical (SC) results do not include the quantum correction to the partition function for motion in the transition

vector (tunneling, eq. 7) whereas the quantum-corrected (QC) results do. The MD simulations that generated the snapshot configurations from the local relaxations to minima or saddle points were initiated were performed at 363 K, so the frozen solvent environments should sample a distribution representative of that temperature, corresponding to the conditions of the experimental determination of $k(^1H_3)/k(^2H_3)$.[16] However, once each Hessian has been computed, it may be used to evaluate IPFRs and KIEs at any temperature: 300 K is considered in order to facilitate comparison with our earlier work.[1] The value given for each KIE is the quotient $\langle f_{RS}\rangle/\langle f_{TS}\rangle$ of average IPFRs evaluated for all the RS and TS configurations. Of course, $\langle f_{RS}\rangle$ and $\langle f_{TS}\rangle$ each have a mean and a standard deviation: the results in Table 4 show mean values with their uncertainties given to $\pm 1\sigma$. The average KIEs are presented uniformly with 3 decimal places, even where the implied precision is not strictly justified by the magnitude of the uncertainty; this helps to identify where two results are numerically different even though they are indistinguishable within their uncertainties. It is appropriate to discuss the AM1/TIP3P results first and then B3LYP/6-31G* results.

The first row of data entries in Table 4 contains results obtained using AM1 as the QM method for the nucleophile H_2O and electrophile CH_3Cl surrounded by TIP3P water molecules: the Hessian includes only these 8 atoms, and all other solvent molecules are frozen. The 65 RS structures are reactant-like local energy minima actually obtained by relaxation from an initial 100 "TS" configurations, most of which did not converge towards a saddle point; the 9 TS structures are the few which did converge to a saddle point in this instance. The average value for $k(^1H_3)/k(^2H_3) = 0.80 \pm 0.05$ is inverse and accords with the range of values reported in Table 1 for the entries "AM1 #1" to "AM1 #5" previously obtained for TS and RS pairs connected by an intrinsic reaction coordinate path, although it may be seen that a couple of those KIEs lie outside $\pm 2\sigma$ of the present mean. Figure 2 shows the distribution of all possible individual KIEs, each obtained as the quotient f_{RS}/f_{TS}, for all possible pairs of 65 RSs and 9 TSs at 300 K: the full range of values extends from < 0.66 to > 1.00 and includes all the previous AM1 values.

The second row in Table 4 is similar to the first, but with the KIEs evaluated at 363 K. As expected, each KIE is smaller (closer to unity) than at the lower temperature. The average value for $k(^1H_3)/k(^2H_3) = 0.84 \pm 0.04$ is still inverse and may be compared with the experimental value of 0.92 at 90 °C.[16] (Consideration of the quoted errors on the individual rate constants $k(^1H_3)$ and $k(^2H_3)$ suggests an uncertainty of about ± 0.01 for the experimental value.) The AM1 calculated value differs from the experimental value by about 3σ, meaning that it is very likely to be incorrect. The tunnelling correction is negligible in magnitude.

Row 3 in Table 4 contains results for 100 RSs obtained with an extended QM region containing chloromethane and the water nucleophile but also a variable number (up to 8) of additional first-solvation-shell water molecules selected by a distance criterion, all of which were included in the Hessian. The mean value of the 2° α-$^2H_3$ KIE is a bit larger (more inverse) than that shown in row 2, and the standard deviation is a little lower, perhaps reflecting the larger number of RS configurations sampled. Since Tables 2 and 3 suggest that inclusion of first-solvation-shell waters may tend to make this KIE less inverse by virtue of a kinetic energy effect, it is possible that the (slightly) more inverse result here might reflect changes in the Hessian due to polarization of the extra QM waters, *i.e.* a potential energy effect.

Rows 5 and 6 in Table 4 contains results obtained using B3LYP/6-31+G(d,p) as the QM method for the nucleophile H_2O and electrophile CH_3Cl surrounded by TIP3P water molecules: again the Hessian includes only these 8 atoms, and all other solvent molecules are frozen. The 81 RS structures are reactant-like local energy minima obtained also by relaxation from an initial 100 "TS" configurations, only 14 of which did converge to a saddle point. The average value for $k(^1H_3)/k(^2H_3) = 0.91 \pm 0.05$ at 363 K is in satisfying agreement with the experimental value 0.92 ± 0.01, and the distribution of calculated KIEs for all possible individual RS/TS pairs (Figure 3) shows that the range of the computational results encompasses the experiment. Better statistics would be obtained from a larger sample of computed solvent configurations, particularly for the transition state.

The final row of calculated results in Table 4 refers to 56 RSs obtained with only chloromethane in the QM region and all waters being MM; the Hessian contains only CH_3Cl. The average 2° α-$^2H_3$ KIE is more inverse than when the nucleophilic water is included in the hessian, but the difference is equivalent to only 1σ of the standard deviation. It is not clear whether this is a kinetic energy or a potential energy effect.

Although (as far as we are aware from the literature) the 1° ^{14}C and ^{37}Cl KIEs have not been determined for chloromethane hydrolysis, nonetheless we include calculated average values for $k(^{12}C)/k(^{14}C)$ and $k(^{35}Cl)/k(^{37}Cl)$ in Table 4. It is to be hoped that experimental values might yet be determined. The magnitudes and directions of the calculated values appear to be completely reasonable, especially as obtained with the B3LYP/6-31+G(d,p) method in combination with TIP3P. Note that there is a substantial quantum correction to the ^{14}C KIE, suggesting a significant tunneling contribution to the isotope effect.

The energetics of chloromethane hydrolysis have been determined at the B3LYP/6-31G* level with continuum solvation (PCM):[17,18] the calculated Gibbs energy of activation $\Delta^{\ddagger}G$ = 118 kJ mol^{-1}

reported by Martínez *et al.*[17] agrees well with the experimental value of 117 kJ mol^{-1} [19] but it is unclear why Ruff and Farkas reported $\Delta^{\ddagger}G$ = 121.2 kJ mol^{-1} as agreeing well with an experimental value of 126.7 kJ mol^{-1} attributed to the same source. The structural parameters for the S_N2 TS in PCM water also differ somewhat. Martínez *et al.*[17] found the leaving group C···Cl and nucleophile O···C distances to be 2.457 Å and 1.779 Å , respectively, whereas Ruff and Farkas reported 2.425 Å and 1.904 Å , respectively. Analysis of our B3LYP/6-31+G(d,p)/TIP3P TSs yields average values C···Cl = 2.285 ± 0.063 Å and O···C = 2.016 ± 0.070 Å, with the angle O···C···Cl = 176.2° ± 2.3°.

Aida and Yamataka[20] computed 2° α-$^2H_3$ and 1° ^{13}C KIEs for chloromethane hydrolysis at 363 K using the HF/6-31+G* method with 3, 4, 10 and 13 water molecules in gas-phase clusters. In each case a single TS was connected to a single RS by means of an intrinsic reaction coordinate path, and all waters were treated as QM. As the number of water molecules increased, so the calculated $k(^1H_3)/k(^2H_3)$ became less inverse: 0.877, 0.868, 0.907 and 0.936. This trend seems to agree with that shown in Table 3, but note that Aida and Yamataka's results involve a different Hessian and a different geometrical structure for different number of water molecules. Moreover, there is only a single RS and TS structure for each number of water molecules. The $k(^{12}C)/k(^{13}C)$ values in the range 1.043 to 1.047 reported by these authors do not vary much with the number of waters and are consistent with our ^{14}C KIEs.

A QM/MM simulation has been performed for chloromethane hydrolysis is supercritical water.[21] The temperature (600 K) and density (0.33 g cm^{-3}) used in this study are completely from those in this work, and kinetic isotope effects were not reported.

Conclusions

Computational simulations for chloromethane hydrolysis performed using QM/MM methods with explicit solvation by large numbers of water molecules have yielded results of two kinds. First, we shown that for accurate calculations of KIEs in solvated systems should involve a subset Hessian including the substrate together with any solvent atoms making specific interactions with any isotopically substituted atom. Second, the ensemble-averaged 2° α-$^2H_3$ KIE calculated with the B3LYP/6-31+G(d,p)/TIP3P method is in good agreement with experiment. This comparison is meaningful because it includes consideration of uncertainties owing to sampling of a range of representative thermally-accessible solvent configurations.

Methods

A cutoff rule for KIEs of reactions in aqueous solution

QM/MM calculations were performed by means of the CHARMM,[22,23] GAMESS-UK[23,24] and GRACE[2,25] programs. Chloromethane and the nucleophilic water molecule were treated by the AM1 method[26] or the B3LYP density functional[27] with the 6-31+G(d,p) basis set, and 496 solvent water molecules in a surrounding sphere (radius 15 Å) were described by the flexible TIP3P MM potential[28] within CHARMM. Geometry optimisations were carried out for a representative minimum energy structure of the reactant complex (RC) and for a representative transition structure (TS) corresponding to a first-order saddle point on the energy hypersurface. Vibrational hessians were computed for a specified subset of N_s atoms including the QM atoms and those of a selected number of MM water molecules. Our CAMVIB and CAMISO programs were employed, first to remove translational and rotational contributions from computed subset Hessians by a projection method,[29,30] and second to evaluate partition functions for translation, rotation and vibration (for $3N_s - 6$ internal degrees of freedom) of the subset atoms, and thence KIEs, within the harmonic-oscillator, rigid-rotor, ideal-gas approximations and the standard semi-classical transition-state theory of isotope effects.[14]

Ensemble–averaged KIEs for reactions in aqueous solution

The MP2/6-31+G(d,p)/PCM optimized (GAUSSIAN09)[31] transition structure $[H_2O\cdots CH_3\cdots Cl]^{\ddagger}$ was placed at the centre of a cubic box (side 31.4 Å) of pre-equilibrated TIP3P water, from which those with oxygen closer than 2.8 Å to any QM atom were removed. The 8 QM atoms were now described by the AM1 Hamiltonian and the MM region contained 3090 atoms. With the QM atoms frozen, energy minimization was carried out employing LBFGS methods until a convergence in the gradient of 0.1 kJ mol^{-1}. The system was further relaxed by means of a 500 ps QM/MM MD simulation (DYNAMO)[32] at 363 K with all atoms free to move except that the O···C and C···Cl distances were constrained. Periodic boundary conditions were used, keeping the number of molecules (and the density) constant under Langevin-Verlet NVT conditions correspond to the canonical ensemble. The cut-offs for all kind of interactions were established in 15.5, 14.0 and 12.5 Å, and the time step was 1 fs. A further 1 ns QM/MM MD simulation was then performed for the constrained transition state. Chloromethane (QM) in water (MM) was also treated similarly as a reactant state.

100 structures were taken at 10 ps intervals along these MD trajectories, each with a different and representative solvent configuration, and for each of these a subset of atoms was then relaxed by means to a local stationary point within a frozen solvent environment, using a combination of GRACE and DYNAMO, and a Hessian was computed for each. The subset atoms were treated as QM, and were

described by both AM1 and B3LYP/6-31+G(d,p) methods. Their IPFRs were determined treating both the internal and external degrees of freedom as harmonic vibrational modes, by means of our UJISO program[33] and KIEs were evaluated at both 300 K and 363.15 K.

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References

1 G. D. Ruggiero, I. H. Williams, *Abstr. 8th Kyushu Intl. Symp. Phys. Org. Chem*., Kyushu University, Japan, 1999.

2 A. J. Turner, V. Moliner, I. H. Williams, *Phys. Chem. Chem. Phys*. **1999**, *1*, 1323-1331.

3 R. L. Heppolette, R. E. Robertson, *Proc. Roy. Soc. (London) A* **1959**, *252*, 273-285.

4 R. E. Robertson, A. Annesa, J. M. W. Scott, *Can. J. Chem*. **1975**, *53*, 3106-3115.

5 J. J. Ruiz-Pernía, I. H. Williams, *Chem. Eur. J*. **2012**, *18*, 9405-9414.

6 (a) M. Wolfsberg, M. J. Stern, *Pure Appl. Chem*. **1964**, *8*, 225−242. (b) M. J. Stern, M. Wolfsberg, *J. Chem. Phys*. **1966**, *45*, 4105−4124.

7 E. K. Thornton, E. R. Thornton, in *Isotope Effects in Chemical Reactions*, C. J. Collins, N. S. Bowman, Eds., Van Nostrand Reinhold, New York, **1970**.

8 J. A. Barnes, I. H. Williams, *Chem. Commun*. **1996**, 193-194.

9 V. López-Canut, J. J. Ruiz-Pernía, I. Tuñón, S. Ferrer, V. Moliner, *J. Chem. Theory Comput*. **2009**, *5*, 439–442.

10 E. B. Wilson, D. C. Decius, P. C. Cross, *Molecular Vibrations*, McGraw-Hill, New York, **1955**.

11 O. Redlich, *Z. physik. Chem*. **1935**, *B28*, 371; E. Teller, quoted by W. R. Angus, C. R. Bailey, J. B. Hale; C. K. Ingold, A. H. Leckie, C. G. Raisin, J. W. Thompson, C. L. Wilson, *J. Chem. Soc.* **1936**, 971-987.

12 I. H. Williams, *J. Chem. Theor. Comput.* **2012**, *8*, 542-553.

13 Q. Cui, M. Karplus, *J. Chem. Phys*. **2000**, *112*, 1133-1149.

14 (a) *Isotope Effects in Chemical Reactions*, eds. C. J. Collins, N. S. Bowman, Van Nostrand Reinhold, New York, **1970**. (b) L. Melander, W. H. Saunders, *Reaction Rates of Isotopic Molecules*, Wiley, New York, **1980**.

15 G. D. Ruggiero, S. J. Guy, S. Martí, V. Moliner, I. H. Williams, *J. Phys. Org. Chem.* **2004**, *17*, 592 – 601.

16 J. A. Llewellyn, R. E. Robertson and J. M. Scott, *Can. J. Chem*. **1960**, *38*, 222-232.

17 A. G. Martínez, E. Teso Vilar, J. Osío Barcina, S. de la Moya Cerero, *J. Org. Chem*. **2005**, *70*, 10238-10246.

18 F. Ruff, Ö. Farkas, *J. Phys. Org. Chem*. **2008**, *21*, 53-61.

19 M. H. Abraham, D. J. McLennan, *J. Chem. Soc*., *Perkin 2*, **1977**, 873-879.

20 M. Aida and H. Yamataka, *J. Mol. Struct., Theochem* **1999**, 461-462, 417-427.

21 T. Hori, H. Takahashi, T. Nitta, *J. Chem. Phys.* **2003**, *119*, 8492-8499.

22 B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, M. Karplus, *J. Comput. Chem.* **1983**, *4*, 187.

23 GAMESS-UK/CHARMM was a coupling of GAMESS-UK 6.2 and CHARMM c27b2 by P. Sherwood, E. M. Billings, B. R. Brooks: *cf.* D. Das, K. P. Eurenius, E. M. Billings, P. Sherwood, D. C. Chatfield, M. Hodoscek, B. R. Brooks, *J. Chem. Phys.* **2002**, *117*, 10534-10547.

24 GAMESS-UK, Daresbury Laboratory, 1995-9. M. F. Guest, J. H. van Lenthe, K. Schoffel, P. Sherwood, R. J. Harrison, with contributions from: R. D. Amos, R. J. Buenker, M. Dupuis, N. C. Handy, I. H. Hillier, P. J. Knowles, V. Bonacic-Koutecky, W. von Niessen, V. R. Saunders, A. J. Stone. The package is derived from the original GAMESS code due to M. Dupuis, D. Spangler, J. Wendoloski.

25 (a) V. Moliner, A. J. Turner, I. H. Williams, *Chem. Commun*. **1997**, 1271-1272. (b) A. J. Turner, PhD thesis, University of Bath, 1997.

26 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.

27 (a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789. (b). A. D. Becke, *J. Phys. Chem.* **1993**, *98*, 5648-5652.

28 W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey and M. L. Klein, *J. Chem. Phys*. **1983**, *79*, 926-935. Note that CHARMM contains a modified TIP3P potential that includes intramolecular terms: A. D. MacKerell, D. Bashford, R. L. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo, S. Ha, D. Joseph-McCarthy, L. Kuchnir, K. Kuczera, F. T. K. Lau, C. Mattos, S. Michnick, T. Ngo, D. T. Nguyen, B. Prodhom, W. E. Reiher,

B. Roux, M. Schlenkrich, J. C. Smith, R. Stote, J. Straub, M. Watanabe, J. Wiorkiewicz-Kuczera, D. Yin, M.Karplus, *J. Phys. Chem*. **1998**, *102*, 3586-3616.

29 (a) I. H. Williams, *Chem. Phys. Lett.* **1982**, *88*, 462-466. (b) I. H. Williams, *J. Molec. Struct., Theochem* **1983**, *94*, 275-284.

30 (a) I. H. Williams, *J. Am. Chem. Soc*. **1984**, *106*, 7206-7212. (b) I. H. Williams, *J. Chem. Soc., Chem. Commun*. **1985**, 510-511.

31 Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

32 M. J. Field, M. Albe, C. Bret, F. Proust-De Martin, A. Thomas, *J. Comput. Chem.* **2000**, *21*, 1088-1100.

Table 1. QM/MM calculated activation enthalpies (kJ mol^{-1}) and 2° α-$^2H_3$ KIEs for H_2O + CH_3Cl (QM) surrounded by *n* TIP3P water molecules.

QM method	*n*	$\Delta^{\ddagger}H$	$k(^1H_3)/k(^2H_3)$	E^{TS}_{total}
MP2/6-31G*	200	104	0.899	
HF/6-31G*	200	52	0.953	
HF/3-21G	200	12	0.918	
AM1 #1	496	178	0.828	-25699.4
AM1 #2	496	172	0.784	-25696.0
AM1 #3	496	166	0.918	-25696.7
AM1 #4	496	161	0.907	-25696.0
AM1 #5	496	152	0.820	-25700.2
expt. (25 °C)		111[b]	0.93[c]	

[b] Ref. 3.

[c] Ref. 4.

Table 2. QM/MM calculated KIEs (25 °C) and contributing factors for $H_2O + CH_3Cl$ (AM1) surrounded by 496 TIP3P water molecules, of which N_w are included in the Hessian.

N_w	$k(^1H_3)/k(^2H_3)$				$k(^{12}C)/k(^{14}C)$				$k(^{35}Cl)/k(^{37}Cl)$			
	KIE	MMI	EXC	ZPE	KIE	MMI	EXC	ZPE	KIE	MMI	EXC	ZPE
104	0.838	1.000	0.986	0.849	1.122	1.001	1.024	1.096	1.007	1.000	1.004	1.003
72	0.838	1.000	0.987	0.849	1.122	1.001	1.024	1.096	1.007	1.000	1.004	1.003
43	0.838	1.000	0.986	0.849	1.122	1.001	1.024	1.096	1.007	1.000	1.004	1.003
23	0.839	1.000	0.985	0.851	1.122	1.001	1.024	1.096	1.008	1.002	1.003	1.003
13	0.837	1.003	0.985	0.846	1.122	1.003	1.021	1.097	1.008	1.003	1.002	1.003
6	0.840	1.002	0.994	0.843	1.124	1.002	1.018	1.103	1.008	1.000	1.003	1.005
3	0.835	1.012	0.989	0.834	1.124	1.011	1.008	1.103	1.008	0.999	1.003	1.006
2	0.865	1.016	1.047	0.813	1.124	1.026	1.004	1.103	1.009	0.996	1.004	1.009
1	0.839	1.028	1.064	0.767	1.123	1.017	1.012	1.092	1.009	0.993	1.006	1.010
0	0.838	0.880	1.204	0.791	1.124	1.037	0.999	1.085	1.009	0.998	1.002	1.009

Table 3. QM/MM calculated KIEs (25 °C) and contributing factors for $H_2O + CH_3Cl$ (B3LYP/6-31G*) surrou
molecules, of which N_w are included in the Hessian.

N_w	$k(^1H_3)/k(^2H_3)$				$k(^{12}C)/k(^{14}C)$				$k(^{35}Cl)/k(^{37}Cl)$		
	KIE	MMI	EXC	ZPE	KIE	MMI	EXC	ZPE	KIE	MMI	EXC
60	0.934	0.999	1.035	0.904	1.111	1.001	1.025	1.083	1.006	1.000	1.004
30	0.935	1.000	1.036	0.902	1.111	1.001	1.025	1.083	1.006	1.000	1.004
15	0.935	1.001	1.032	0.905	1.112	1.001	1.024	1.085	1.006	1.000	1.004
10	0.934	0.999	1.037	0.902	1.114	1.002	1.020	1.090	1.006	1.000	1.003
5	0.936	1.000	1.035	0.904	1.114	1.002	1.018	1.092	1.006	1.000	1.003
2	0.943	1.005	1.017	0.921	1.117	1.003	1.014	1.098	1.006	1.000	1.003
0	0.887	0.926	1.114	0.861	1.109	1.023	1.006	1.078	1.007	0.999	1.001

Table 4. QM/MM calculated KIEs for H_2O + CH_3Cl (QM) surrounded in TIP3P water.

QM	T /K	number of waters in RS Hessian	number of structures		$k(^1H_3)/k(^2H_3)$		$k(^{12}C)/k(^{14}C)$	
			RS	TS	SC	QC	SC	QC
AM1	300	1	65	9	0.798 ± 0.050	0.799 ± 0.050	1.155 ± 0.005	1.174 ± 0.011
	363	1	65	9	0.841 ± 0.040	0.842 ± 0.040	1.064 ± 0.004	1.090 ± 0.014
	363	1 – 9	100	9	0.834 ± 0.034	0.835 ± 0.034		
B3LYP	300	1	81	14	0.891 ± 0.058	0.891 ± 0.058	1.107 ± 0.007	1.120 ± 0.007
	363	1	81	14	0.907 ± 0.048	0.909 ± 0.048	1.094 ± 0.005	1.103 ± 0.006
	363	0	56	14	0.874 ± 0.036	0.874 ± 0.036		
Expt.[a]	363				0.92 ± 0.01			

[a] Ref. 16

Figure 1. QM region (H_2O + CH_3Cl, ball and stick) in a sphere (of radius 15 Å) comprising 496 MM water molecules, of which 104 (ball and stick) are included in the Hessian.

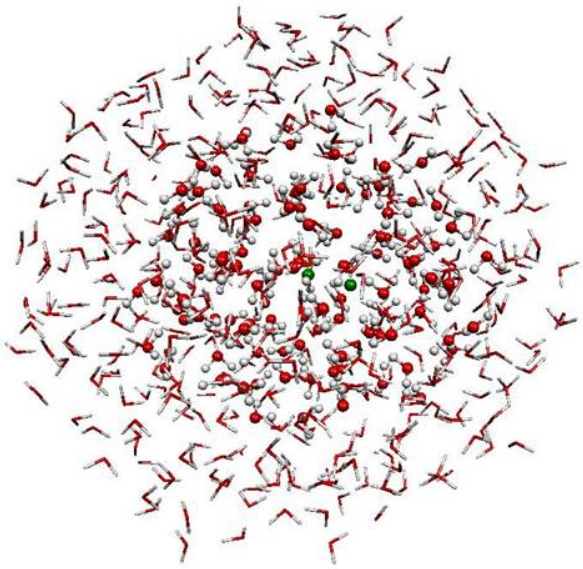

Figure 2. Distribution of α-$^2H_3$ KIEs obtained from all possible pairs of 65 RSs and 9 TSs with the AM1/TIP3P method at 300 K.

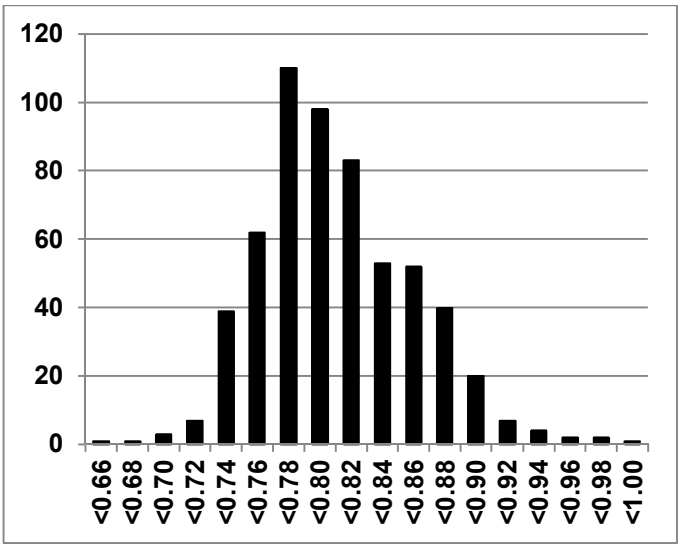

Figure 3. Distribution of α-$^{2}H_3$ KIEs obtained from all possible pairs of 65 RSs and 9 TSs with the B3LYP/6-31+G(d,p)/TIP3P method at 363 K.